Valproic acid use in pregnancy and congenital malformations (reply)

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THE AUTHORS REPLY: Okamoto suggests that determining whether there are differences in titers of autoantibodies and epitope specificity in Goodpasture's disease on the basis of lung involvement might be beneficial for understanding the mechanism of this disease. In one study, patients with Goodpasture's disease who had positive results for both ANCA and anti-GBM antibodies had a poor prognosis when they presented with severe renal failure.[1] Other studies reported no difference between patients with ANCA and those without ANCA with respect to the NC1-antigen specificity of anti-GBM antibodies.[2] In our study, 12 of 46 patients had lung hemorrhage. However, there was no difference in autoantibody titers between patients with hemorrhage and those without hemorrhage. Furthermore, despite the earlier suggestion that the prognosis for double-positive patients may be dependent on both populations of antibodies,[3] we did not find any difference between patients with ANCA and those without ANCA in titers of circulating anti-α3NC1 or anti-α5NC1 autoantibodies. Our analysis of antibody epitopes indicates that conformational changes occur in collagen IV α345NC1 with no difference in the presence of concomitant ANCA. Thus, any influence of ANCA on the severity of lesions among patients with Goodpasture's disease does not appear to be mediated by changes in epitope conformation.

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Since publication of their article, the authors report no further potential conflict of interest.

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Valproic Acid Use in Pregnancy and Congenital Malformations

TO THE EDITOR: In their article describing valproic acid monotherapy in pregnancy and major congenital malformations (June 10 issue),[1] Jentink and colleagues concluded by recommending that the use of valproic acid be avoided, if possible, in women of childbearing potential. However, this study did not assess the effect of the dose of valproic acid on the risk of birth defects. In many patients with primary generalized epilepsy, the condition is well controlled with the use of low doses of valproic acid (<1000 mg). Among pregnant women in the Australian Pregnancy Register, the risk of teratogenic effects was not significantly higher with valproic acid than with alternative antiepileptic drugs, and seizure control was better in patients treated with valproic acid than in those treated with lamotrigine or carbamazepine, in any trimester of pregnancy.[2] Seizures endanger the mother as well as the fetus. We believe that a more appropriate conclusion is that high doses of valproic acid should not be used as a first-choice drug in women of childbearing potential.

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1. Jentink J, Loane MA, Dolk H, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med 2010;362:2185-93.
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THE AUTHORS AND A COLLEAGUE REPLY: As we mentioned in our article, we did not have information on doses of valproic acid; therefore we cannot draw any conclusion about doses of valproic acid and the risk of congenital malforma-

tions. We think that caution should be exercised when conclusions are drawn about doses of valproic acid given during pregnancy. The study by Vajda and colleagues had a relatively small sample (113 pregnancies involving in utero exposure to valproic acid monotherapy) and did not include information on specific malformations.[1] In a study including 715 pregnancies involving exposure to valproic acid monotherapy, the mean maternal daily dose of valproic acid did not differ significantly between the offspring without malformations and those with malformations.[2] A higher prevalence of congenital malformations has also been noted in association with lower doses of valproic acid, as compared with other antiepileptic drugs.[1,2] Case–control studies including large numbers of pregnancies in which there is exposure to a range of doses of valproic acid and including information about specific malformations could help inform whether a low dose of valproic acid is safe in terms of the risk of congenital malformation.[3]

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Since publication of their article, the authors report no further potential conflict of interest.

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Early Alzheimer's Disease

TO THE EDITOR: The example of a 72-year-old man with memory problems in the article by Mayeux (June 10 issue)[1] suggests both the complexities of diagnosing Alzheimer's disease and the idea that older patients are now likely to be employed. As the world's population ages, these are issues with which all physicians will need to become familiar. Many of the appropriate interventions are nonpharmacologic; Mayeux addresses this subject comprehensively with respect to driving, but he does not mention other interventions. Our own practice is to advise all patients presenting with memory problems and their families to consider a durable power of attorney. Most states have legislated for a specific legal representation, the health care proxy who may make decisions should the patient become incapacitated.[2] Advance care directives are an alternative, but ethical concerns remain with respect to their applicability.[3] The use of health care proxies sidesteps some of these issues and should be included in the advice offered to these patients.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Although many of the diagnostic and practical dilemmas of early Alzheimer's disease are covered in the Clinical Practice article by Mayeux, an outstanding area of concern is the effect of early Alzheimer's disease on occupation. In societies with healthier older people and abolition of mandatory retirement,[1] clinicians who care for patients with dementia are presented increasingly with patients (such as the investment manager in the case vignette in the article) whose jobs demand high levels of performance.

Discussion with the patient, encouraging him or her to talk about ongoing work with occupational health services or the employer, is an initial pragmatic step. However, there is an urgent need for joint development of solutions by occupational health specialists, geriatricians, and neurologists regarding continued working and early dementia; these solutions should preserve inde-